SUMMARY OF SAFETY AND PROBABLE BENEFIT

I. GENERAL INFORMATION

Device Generic Name: Interactive Wound and Burn Dressing

Device Trade Name: Composite Cultured Skin

Applicant's Name and Address: Ortec International, Inc.
3960 Broadway, 2nd Flr.
New York City, NY 10032

Humanitarian Device Exemption Number: H990013

Date of Humanitarian Use Device Designation: April 24, 1998

Date of Panel Recommendation:
Composite Cultured Skin was not submitted to the General and Plastic Surgery Devices Panel for review (refer to Section XI for discussion).

Date Of GMP Inspection:
Ortec International Inc.: September 28, 2000
Steris Isomedix: August 28, 2000
Kensey Nash Corp.: October 5, 2000

Date Of Notice of Approval of Application: FEB 2 1 2001

II. INTENDED USE / INDICATIONS

Composite Cultured Skin (CCS) is indicated for use in patients with mitten hand deformity due to Recessive Dystrophic Epidermolysis Bullosa (RDEB) as an adjunct to standard autograft procedures (i.e., skin grafts and flaps) for covering wounds and donor sites created after the surgical release of hand contractions (i.e., "mitten" hand deformities).

III. DEVICE DESCRIPTION

Composite Cultured Skin is composed of a collagen matrix in which allogeneic human skin cells, (i.e., epidermal keratinocytes and dermal fibroblasts) are cultured in two distinct layers. The collagen cross-linked sponge consists primarily of Type I bovine collagen laminated on one side with a thin gel layer of acid-soluble bovine collagen.

The device is manufactured under aseptic conditions with cells derived from human neonatal foreskin tissue. The fibroblast and keratinocyte cells are tested for human viruses, retroviruses, bacteria, fungi, yeast, mycoplasma, karyology, isoenzymes and

tumorigenicity. The final product is tested for morphology, cell viability, cell density, sterility, mycoplasma, and physical container integrity. Product manufacture also includes reagents derived from animal materials including bovine pituitary extract. All animal derived reagents are tested for viruses, bacteria, fungi, yeast, and mycoplasma before use and all bovine material is obtained from countries free of Bovine Spongiform Encephalopathy (BSE).

The device measures approximately 6 cm x 6 cm (minimally 36 cm^2). A non-adherent mesh (N-Terface® (Winfield Laboratories, Inc., Dallas, Texas)) is placed on both aspects of the device to protect the cells. The device is packaged in a plastic tray with protein-free packaging medium containing DMEM, water for irrigation, sodium bicarbonate, folic acid solution, HEPES buffer, L-Glutamine, MEM non-essential amino acids, and sodium hydroxide to maintain cell viability during storage and shipping.

The plastic tray is sealed within a peelable inner pouch to provide a sterile barrier against moisture and gas. The inner pouch is, in turn, sealed inside a heavier-gauge outer pouch that protects the inner pouch sterility barrier and the product against damage during shipment. The multi-stage packaged product is packed with pre-chilled gel packs and shipped to the destination in a padded and insulated shipping container that maintains a temperature of 11-19° C (for up to 72 hr.).

IV. CONTRAINDICATIONS

- Composite Cultured Skin is contraindicated for use on clinically infected wounds (see Precautions).
- Composite Cultured Skin is contraindicated as the primary coverage of web spaces and phalangial metacarpal joints during hand reconstructive surgery.
- This product may contain trace amounts of penicillin, streptomycin, and fungizone (amphotericin B) used during cell processing. Avoid the use of this product in patients known to be allergic to these materials.

The Warnings and Precautions can be found in the professional labeling.

V. ADVERSE EFFECTS OF THE DEVICE ON HEALTH

A. Epidermolysis Bullosa

The reported adverse events, which occurred in the studies evaluating CCS in RDEB patients with mitten hand deformities as an adjunct to standard autograft procedures and in the treatment of chronic ulcers in EB patients, at an incidence rate of greater that 1% are listed in Table 1. Because each patient in these studies received both CCS and standard care treatments on different wounds, the causality for systemic adverse events cannot be determined. Thus, the data below are presented with regard to the incidence of adverse events at treatment and control sites (i.e., local events on a per patient basis) and systemic adverse events.

Table 1 Adverse Events with an Incidence of Greater Than 1%Epidermolysis Bullosa Studies in U.S. and Australia

Adverse Event	Study Site Involvement		Systemic (n=19)
	CCS (n=19)	Control (n=24)*	
Fever	0 (0.0%)	0 (0.0%)	4 (21.0%)
Constipation	0 (0.0%)	0 (0.0%)	3 (15.7%)
Vomiting	0 (0.0%)	0 (0.0%)	3 (15.7%)
Pain	2 (10.5%)	0 (0.0%)	1 (5.2%)
Nausea	0 (0.0%)	0 (0.0%)	2 (10.5%)
Redness (total body)	0 (0.0%)	0 (0.0%)	1 (5.2%)
Erythema (non-study site)	0 (0.0%)	0 (0.0%)	1 (5.2%)
Edema (non-study site)	0 (0.0%)	0 (0.0%)	1 (5.2%)
Infection (Upper Respiratory)	0 (0.0%)	0 (0.0%)	1 (5.2%)
Squamous Cell Carcinoma (non-study site)	0 (0.0%)	0 (0.0%)	1 (5.2%)

* In the U.S. study involving 12 patients, there were 2 control sites per patient (acellular collagen sponge and standard care).

There were no incidences of wound infection, delayed wound healing or cellulitis associated with the use of CCS or the control sponge (acellular collagen sponge) in this patient population.

B. All CCS Treated Patients

The adverse effects observed during clinical evaluations of CCS patients with EB, as well as in other studies include a total of 8 deaths and 71 non-fatal serious adverse events in 186 patients. The non-fatal serious adverse events observed in patients treated with CCS are shown in Table 2. These adverse events were observed in seven clinical studies (including E.B.) and include a broader study population, some with systemic disorders, such as deep partial and full thickness burns. Of the 186 patients for which safety data are available, 82 (44%) had at least one adverse event reported. The adverse events with the highest incidence levels were constipation 26 (13.9%), pain 24 (12.9%), fever 19 (10.2%), pruritis 14 (7.5%) and anemia 13 (6.2%). None of these adverse events (including the non-fatal serious adverse events) were judged by the treating investigator as definitely related to CCS application.

Table 2. Serious Adverse Events observed in all patients treated with CCS (N=186).

SERIOUS ADVERSE EVENTS	# OF EVENTS
Sepsis	3
ARDS	3
Renal Failure	2
Pneumothorax*	2
Pneumonia	2

Hypotension	3
Leg Clots	1
Surgical Interventions:	-
Hernia Repair	1
Knee	1
Hip	2
Periodontal	1
Hand	1
Thoracotomy	1
Femoral Artery*	1
Infarction	1
Chest Pain	1
Cellulitis	2
Reconstructive Surgeries	9
Intubation	4
Non-Healing Wound*	3
Admission to Rehab Facility	5
Infection	3
Contracture Release	9
CHF	1
Minor Stroke	1
Seizure Disorder	1
Autograft (Non-CCS Site)*	3
Squamous Cell Carcinoma	1
Multi System Organ Failure	1
Necrosis to Musculature Around Femoral Artery*	1
Bleed at Femoral Artery*	1
TOTAL SERIOUS ADVERSE EVENTS	**71**

* One of these events in each of these categories is related to the control treatment site.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The standard treatment for healing of wounds on RDEB patients includes the use of non-adherent dressings for wound coverage or surgical alternatives such as autologous skin flaps and/or split thickness skin grafts[1,2]. Impaired wound healing, infection risk and donor site scarring can occur in RDEB patients after harvesting of split thickness donor grafts after treatment with standard non-adherent wound dressings. Thus, the use of CCS as an adjunct to skin flaps and split thickness autografts provides probable benefit to patients by reducing the number and size of donor sites required after hand reconstruction surgery, thereby reducing the risk of associated complications.

VII. MARKETING HISTORY

CCS has not been marketed previously.

VIII. SUMMARY OF PRE-CLINICAL STUDIES

The biocompatibility of CCS and its components were verified through a series of *in vitro* and *in vivo* tests. Because there is no good animal model for RDEB, the ability of the device to promote wound healing was demonstrated in a standard acute wound model in mice.

A. The biocompatibility studies.

The biocompatibility of the collagen sponge component of the device was demonstrated by the following tests:

1. *In vitro analyses*

- Hemolytic effect – A phosphate-buffered saline (PBS) extract of the collagen sponge was non-hemolytic to rabbit red blood cells.
- Cytotoxicity – A PBS extract of the collagen sponge coated with collagen gel was non-cytotoxic to L929 mouse fibroblast cells.
- Mutagenicity - The collagen sponge coated with a collagen gel did not produce a mutagenic effect in an Ames Assay.

2. *In vivo analyses*

- Modified Maguire Hypersensitivity test – a PBS extract of the sponge coated with collagen gel did not product an allergic contact dermatitis in guinea pigs following challenge.
- USP XXII Class IV material - The collagen sponge passed all the test requirements.
- Pyrogens – A PBS extract of the collagen sponge coated with collagen gel passed the USP rabbit pyrogen test.
- Resorption - Application of the collagen sponge coated with collagen gel (test article) and a Helistat sponge (control article) onto full thickness wounds on pigs, demonstrated that both the test and control articles resorbed within 7 days without disrupting the healing process.
- Implantation – In this test both the finished CCS and the collagen sponge were evaluated. At 7 days post i.m. implantation of the collagen sponge component and CCS, only mild to moderate inflammation was observed microscopically. At 30 days post-implantation both materials displayed a mild inflammatory response and reduced lymphocyte infiltration when compared to the 7 day response. At 90 days there was no evidence of inflammatory response.

B. Shelf life –

The rinsed final product has a shelf life of 72 hours after being packaged for shipping. This expiration date is based upon the extensive experience in US clinical studies and the results of a validation study that evaluated the following device parameters as a function of time: 1) viable cell count, 2) percent cell viability, 3) device sterility, 4) cell metabolic activity and 5) package integrity.

C. Sterility Testing

Composite Cultured Skin is manufactured under aseptic conditions from a sterilized bovine collagen sponge and cells derived from human neonatal foreskin tissue. CCS is shipped following a preliminary sterility test with a 48 hour incubation and a final endotoxin test. After sublot distribution, each lot is tested for: mycoplasma, sterility in the USP 14 day test and CCS structure and cell-morphology (via histology).

The safety of the product was assessed by testing the fibroblast and keratinocyte cells for human viruses, retroviruses, bacteria, fungi, yeast, mycoplasma, karyology, isoenzymes and tumorigenicity. In addition, each lot of animal-derived reagents used in product manufacture are tested for viruses, bacteria, fungi, yeast, and mycoplasma before use and all bovine material is obtained from countries free of Bovine Spongiform Encephalopathy (BSE).

IX. SUMMARY CLINICAL STUDIES

The device has been studied in 4 clinical investigations. Three additional U.S. patients, who were not enrolled in a specific study, also received CCS treatment. One study in the U.S. and one study in Australia enrolled EB patients.

A. **Australian Clinical Study of CCS in the Treatment of EB:** A study of the use of CCS as an adjunct to standard autograft procedures (i.e., skin grafts and flaps) for covering wounds and donor sites created after the surgical release of hand contractions (i.e., "mitten" hand deformities) in patients with RDEB was performed in Australia from 1977 – 1998[3]. In this series, 7 RDEB patients with advanced hand deformities underwent multiple procedures for degloving of mitten deformities. Five of the seven patients had prior contracture release surgeries without the use of CCS and thus provide some comparative information.

1. Control Therapy:
Wounds on 5 patients created after the release of hand contraction were covered with split thickness autografts. In specific, autografts were used to cover web spaces and joints.

2. Treatment:

Seven patients (of which five had previously undergone contraction release surgery without application of CCS) underwent at least 1 hand surgery with subsequent coverage of wounds with a combination of CCS, skin flap and autografts. Autografts and surgical flaps were applied on the hardest-to-heal areas, i.e., the web spaces and joints. When flaps were used, it was always the apex of the web spaces. CCS was applied to any remaining areas on the dorsum of the hand, fingers and to donor sites. CCS was also used as an adjunct to autografts during dressing changes when areas of unepithelialized tissue developed, which eliminated or decreased the need for additional autografts.

After surgery and the first dressing change, a new long lasting custom-made thermoplastic splint was created and fitted by a physiotherapist to maintain fingers in extension and thumb in abduction. Initially, the patient used the splint around the clock. After 6-8 weeks, for the next 12 months an elasticized glove was used over elasticized bandages (COBAND) applied around each finger during the day and switched back to the splint at night.

3. Effectiveness Outcomes:

When CCS was used, the need for donor sites was reduced. In addition, CCS-treated donor sites healed without complications (i.e., delayed wound healing was not observed and excessive analgesic use was not required). In 2 cases, CCS treated donor sites were re-harvested in subsequent surgeries and produced autografts with properties equivalent to autografts of non-treated patients.

a. *Duration of digital functionality* - The time interval between reconstructive surgeries for all seven patients is shown below. These data suggest that the use of CCS and autograft did not decrease the time to re-surgery. However, further comparisons are difficult because all non-CCS surgeries were performed before 1988 and the investigators introduced the use of CCS and surgical flaps at approximately the same time. In addition, the time between surgeries was dependent upon the severity of the patients' disease and their overall health, i.e., not just finger and thumb functionality. Hence the contributions of CCS alone, in patient outcome are difficult to interpret.

   It should also be noted that the ultimate functional result was heavily influenced by: a) patient compliance with a regimen of hand physical therapy under the guidance of a rehabilitation center familiar with EB complications and b) the severity of the disease.

Table 2 Time Between Surgeries

Pt ID#	Surgery #	Left Hand		Right Hand	
		Type of Surgery	Elapsed time between surgeries (months)	Type of Surgery	Elapsed time between surgeries (months)
1	1	Autograft	-	Autograft	-
	2	CCS + Autograft	17		
	3			CCS + Autograft	37
	-	Last Follow-Up	62*	Last Follow-Up	43*
2	1	Autograft	-	Autograft	-
	2	CCS + Autograft	53		
	3			CCS + Autograft	61
	4	CCS + Autograft	54		
	5			CCS + Autograft	52
	6	Autograft	70		
	-	Last Follow-Up	13*	Last Follow-Up	77*
3	1	CCS + Autograft	-		
	2			CCS + Autograft	-
	-	Last Follow-Up	83*	Last Follow-Up	75*
4	1	Autograft	-		
	2			Autograft	-
	3	Autograft	17		
	4	Autograft	46		
	5	Autograft	46	Autograft	102
	6	CCS + Autograft	36	CCS + Autograft	36
	7	CCS + Autograft	24		
	8			CCS + Autograft	49
	-	Last Follow-Up	121*	Last Follow-Up	96*
5	1	Autograft	-	Autograft	-
	2	Autograft	28	Autograft	28
	3	CCS + Autograft	65		
	-	Last Follow-Up	53*	Last Follow-Up	118*
6	1			CCS + Autograft	-
	-			Last Follow-Up	17*
7	1-10	Hand surgeries **	<12	Hand surgeries **	<12
	11	Autograft	-	Autograft	-
	12	Autograft	13		
	13			Autograft	15
	14	Cultured Keratinocytes***	24		
	15			CCS + Autograft	36
	16			CCS + Autograft	28
	-	Last Follow-Up	66*	Last Follow-Up	24*

* The time between last hand surgery and last follow up.

** Pt# 7 underwent 10 initial hand reconstructive surgeries over 7 years before he was referred to the Eisenberg-Llewelyn group. These surgeries did not include the use of autografts or CCS.

*** Recontractures of the hand after one year, but no additional surgeries performed

b. *CCS treatment of donor sites* - The donor sites used to prepare autografts were also treated with CCS. In 13 surgeries, the CCS-treated donor sites healed in two weeks and in one surgery healed in three weeks. The long-term follow up of three patients has shown their donor sites to remain stable and free of blisters for six to ten years. There was no incidence of delayed healing, infection or squamous cell carcinoma in any of the CCS-treated donor sites.

Two autografts were harvested from previously CCS-treated areas and retreated with CCS. These donor areas had been treated 2 and 4 years earlier with CCS. Both donor sites yielded good quality autografts without shearing of the epidermis from the underlying dermis and permitted healing without any complications.

Histological evaluations of biopsies of donor sites treated with CCS revealed that all sites had fully formed epidermis on a regenerated neodermis. Histology of adjacent EB skin showed dermis denuded of epidermis. However, it was determined that the epidermis detached from the dermis during the biopsy procedure which illustrates the fragility of skin on EB patients.

4. Device Safety

a. *Adverse events:* In 13 operations where donor areas were grafted with CCS, there was no significant postoperative pain requiring narcotic analgesics. All patients received prophylactic oral broad-spectrum antibiotic therapy during the first postoperative week and no pathogens were detected in any of the surgically created wounds. All donor site wounds created during the Australian study healed without sequela.

B. United States Clinical Studies with CCS in the Treatment of EB

The safety of CCS in treating EB patients was also assessed in a controlled randomized study conducted in the United States. The study enrolled 12 junctional (JEB) and dystrophic (DEB) epidermolysis bullosa patients with chronic non-healing wounds.

In this within-patient controlled study, three different non-healing chronic wounds on each patient were treated with either: 1) CCS, 2) the collagen sponge component of CCS or 3) standard care. Reapplication of CCS during the first 4 weeks of the study was at the discretion of the investigator. The safety and efficacy assessments were made on study days 7, 14 and 21 as well as weeks 4, 8, 12 and 26. Ten of the twelve patients completed the study, while the remaining two patients discontinued prematurely because: 1) of the development of squamous cell carcinoma, (which the investigator considered to be a pre-existing condition) and 2) non-study compliance.

Effectiveness – no statistically significant differences in the incidence or time to wound healing were observed in comparisons of CCS, the acellular sponge and standard non-adherent dressings at any time point.

Safety - Adverse events reported in this study are described in Table 1 in Section V.

C. United States Clinical Studies for the Treatment of Other Conditions

1. Patients with deep partial/full thickness burns

Twenty-eight patients with full and deep partial thickness burns were enrolled in a multicenter, randomized double-blind study with 52 week follow-up. 15/28 patients completed the study, 2/28 died during the study and 9 were lost to follow-up and 1 patient withdrew consent.

Safety – 21/28 (75%) patients had at least one adverse event. The 3 most common adverse events were fever, constipation and pruritus. None of the events were judged to be definitely or probably related to treatment. 1 scar, 1 inflicted injury, 1 procedural site reaction and the hemorrhage were judged by the investigator as possibly related to treatment. The remaining adverse events were judged to be remotely related. 2 circulatory failure, sepsis, respiratory insufficiency and acute renal failure as well as 1 incidence of inflicted injury and surgical intervention and abdominal pain, fecal incontinence and dyspnea were rated as severe. 2 patients had non-fatal serious AERs. One patient experienced an inflicted injury (hip fracture) and surgical intervention (a hip replacement and colostomy closure). Another patient experienced skin ulceration (of a decubitus scalp ulcer), impaired healing of the scalp ulcer and scarring (hand webbing). The median healing time (100% closure) was significantly shorter after autograft treatment (i.e., 11 days) when compared to CCS treatment (i.e., 59 days).

Death - 2 patients died during the study. One patient died after arrhythmia, respiratory insufficiency, sepsis, acute renal failure and circulatory failure. A second patient died after abdominal pain and dyspnea related to ARDS. Neither death was attributed to treatment with the device.

2. Donor Site Pilot Study

A prospective, single center, open, randomized, controlled trial was initiated to study the effects of CCS on management of split thickness donor sites in burn patients. Seven patients completed the study. One patient died from septic shock and acute multi-system organ failure which was determined by the investigator as unrelated to the study treatments and probably related to the patient's burn injury. Other adverse events reported in this study were:

- 1 patient experienced 6 adverse events including: spontaneous pneumothorax, necrosis to the musculature around the area of the femoral artery adjacent to the

control donor site, conversion of the control donor site to a full thickness wound, excision and re-autografting of the control donor site, an exsanguinating bleed at the left femoral artery and surgical repair of the left femoral artery.

- 1 patient experienced three adverse events including: suspected burn wound septic shock, acute multisystem organ failure and death.
- 1 patient experienced two adverse events including: respiratory distress and intubation.
- 1 patient experienced acute respiratory distress syndrome.

3. Chronic Venous Ulcer Pilot Study

The trial was a randomized, observer-blinded, parallel-group feasibility study in 36 patients with hard-to-heal venous ulcers. Patients in the control group received standard medical care. 15/17 CCS and 12/19 standard of care patients completed the study.

21/36 (58%) patients had at least one adverse event. The three serious adverse events reported in CCS patients were cardiac failure (n=1), surgical intervention (n=1) and hip fracture (n=1). None of the events were judged by investigators as related to CCS application.

The adverse events reported in this study for the CCS and control patients were:

AER	CCS Group n=17	Control n=19
Application site reaction	3 (18%)	6 (32%)
Cellulitis	2 (12%)	0
Edema Peripheral	1 (6%)	1 (5%)
Pain	1 (6%)	1 (5%)
Cardiac Failure	1 (6%)	0
Hypertension	2 (12%)	2 (11%)
Hypotension	1 (6%)	0
Skin ulceration	1 (6%)	0
Surgical intervention	1 (6%)	0
Wound Infection	4 (24%)	3 (16%)

4. Additional Patients Treated with CCS in the United States

a. A 15 day old newborn infant with EB was treated with CCS as an emergency use device. At 6.5 months after treatment the CCS-treated sites remain healed with no incidence of blistering or sloughing.

b. A 28 day old newborn with areas of mixed superficial and deep partial thickness skin loss on the right lower extremity secondary to the loss of blood and trauma to the area with a circumferential wound of the right calf and thigh approximately 90% partial thickness and 10% superficial thickness was treated with CCS as an

emergency use device. Six days after implantation, the newborn was sepsis-free and the CCS treated wound was approximately 30% re-epithelialized. Despite the progression of healing, the child sustained Systemic Inflammatory Response Syndrome (SIRS) from repeated bouts of blood borne septicemia. Additionally, the child had severe respiratory distress syndrome (RDS). The child subsequently died approximately 1 week post application of CCS as a result of RDS and infection. Takedown of the dressings in the morgue showed no indication of primary infection at the level of the leg, and repaired epithelium was noted over the partial thickness loss sites. The investigator and treating neonatologists judged the cause of death as unrelated to device use.

c. Donor sites and chronic wounds on a 16 year old EB patient were treated with CCS as a compassionate use device. The sites were covered with approximately 200 cm^2 of CCS as was a chronic wound area located on the scalp measuring 55 cm^2. By day 7, the donor sites were over 95% closed and by day 10, the sites were 100% closed. No evidence of blistering or sloughing was present and all wounds remained infection-free. No AERs were reported through the 6 month follow-up. At 8 months post CCS application, the patient died because of generalized sepsis after the development of an intestinal obstruction leading to massive bowel ischemia and intestinal necrosis.

D. Immune Response:

Clinical investigations to date have not revealed any significant clinical manifestations of product-related immuological reactions. These clinical data include treatment of 186 patients (including 12 EB patients in the U.S.). Sera drawn from the patients in US studies revealed no antibody responses to bovine Type I collagen. The impact of device application on patients' humoral or cellular immune responses to the allogeneic human cellular components of CCS, i.e., keratinocytes and fibroblasts has not been determined.

X. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINCIAL STUDIES

The pre-clinical safety studies demonstrate the biocompatibility of the device components. The animal studies also demonstrate that the collagen sponge component of the device is rapidly resorbed and does not interfere with wound repair.

The limited clinical data presented are not adequate to definitely establish the safety and effectiveness of the device for the treatment of patients with EB. However, the data do demonstrate that the device can serve as a beneficial adjunct to standard autograft procedures (i.e., skin grafts and flaps) for covering wounds and donor sites created after the release of hand contractions (i.e., "mitten" hand deformities) occurring in patients with RDEB. The adverse events observed with the device are similar (and not of greater severity or frequency) to those reported previously for the proposed patient population.

The standard treatment for healing of wounds created during hand reconstruction surgery of RDEB patients includes the use of non-adherent dressings for wound coverage or surgical alternatives such as autologous skin flaps and/or split thickness skin grafts[1,2]. Impaired wound healing, infection risk and donor site scarring can occur in these patients after harvesting of split thickness donor grafts. Thus, the use of CCS as an adjunct to skin flaps and split thickness autografts provides probable benefit to patients by reducing the number and size of donor sites required after hand reconstruction surgery, thereby reducing the risk of associated complications.

In conclusion, the preclinical safety and performance studies provide reasonable assurance that the device is appropriate for this intended use. The limited clinical data suggest that the device will not expose patients to an unreasonable or significant risk of illness or injury, and that the probable benefit to health from using the device outweighs the risk of injury or illness, especially considering the probable risks and benefits of currently available devices or alternative forms of treatment for this disease.

XI. CDRH DECISION

CRH has determined that, based on the data submitted in this HDE application, Composite Cultured Skin will not expose patients to an unreasonable risk or significant risk of illness or injury, and the probable benefit to health from using the device outweighs the risk of illness or injury. Panel review of this application was not performed because the General and Plastic Surgery Devices Panel had previously provided review and comment on three similar medical devices. An approval order was issued on FEB 21 2001

XII. APPROVAL SPECIFICATIONS

Directions for Use: See the Professional Labeling (Attachment 1)

Warnings, hazards to health with the use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Effects in the Labeling

Information for the Patient: See Patient Labeling (Attachment 2)

Postapproval Requirements and Restrictions: See approval order.

XIII. REFERENCES

1. Scientific American Medicine 2. IX. Vesiculobullous Diseases of the Skin pp. 8-11 (Eds. D.C. Dale and D.D. Federman), Scientific American, Inc. 415 Madison Ave., N.Y., N.Y. 10017

2. "The Treatment of Inherited Epidermolysis Bullosa; Non-molecular Approaches," Chapter 18, in "Epidermolysis Bullosa, Clinical, Epidermologic, and Laboratory Advances and the Findings of the National Epidermolysis Bullosa Registry," Eds. J-D. Fine, E.A. Bauer and J. McGuire (1999), pp 65 – 80.

3. M. Eisenberg and D. Llewelyn, "Surgical management of hands in children with recessive dystrophic epidermolysis bullosa: use of allogeneic composite cultured skin grafts," *British Journal of Plastic Surgery*, 51, 608-613 (1998).